REMARKS

Claims 27-34 are pending.

Applicants respectfully traverse the present rejections.

35 U.S.C. § 101

Claims 27-34 stand rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. Applicants respectfully disagree with the maintained rejection of claims 27-34 for the following reasons.

Applicants' asserted utility should be accepted because it is squarely within the teaching of leading textbooks in the field, and is supported by numerous references and the declarations of skilled experts. This evidence is sufficient to demonstrate utility because an applicants' evidence rebutting the Office's rejection for lack of utility does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility. In addition, the MPEP cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection is sustained only when the applicant asserted a utility "that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." MPEP § 2107.02 III B, citing *In re Gazave,* 379 F.2d 973 (CCPA 1967) (emphasis in original). Such is clearly not the case here. Moreover, **the PTO has recognized that Applicants' asserted utility is sufficient by issuing U.S. Patent No. 7,208,308 (the "'308 patent") with claims supported by the same utility as the utility asserted herein. *See, e.g.* Claim 1 of the '308 patent, which states that the claimed polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors.**

Issuance of the '308 patent is direct and persuasive evidence that Applicants' assertion of utility satisfies the requirements of 35 U.S.C. § 101. In particular, the protocols and

procedures of the gene amplification experiment in the '308 patent (Example 92) and the present application (Example 28) are identical. In addition, the ΔCt values resulting from these gene amplification experiments are similar: 1.0 – 3.82 ΔCt in the '308 patent vs. 1.0 – 2.645 ΔCt in the present application. Further, the Polakis and Scott declarations submitted during prosecution of this application, and relied on by Applicants, also were submitted during prosecution of the '308 patent and accepted by the Office as evidence supporting the asserted utility. Indeed, the declaration of Randy Scott was submitted along with the response that led to issuance of the '308 patent.

Applicants respectfully submit that the issuance of the '308 patent is persuasive evidence that the present application satisfies the utility standard of 35 U.S.C. § 101. Indeed, the '308 patent illustrates that in the PTO's view, the major issue in rejecting the present claims, as stated at page 2 of the Office action mailed March 7, 2007, is overcome.

Moreover, during prosecution of this application, Applicants have provided additional, persuasive evidence that the gene amplification demonstrated in the present application (approximately 87% of lung tumor tissues and approximately 53% of colon tumor tissues listed in Table 9 and tested showed greater than 2-fold DNA amplification) is art recognized to correlate with mRNA levels and polypeptide expression levels. For example, Applicants have cited and relied upon Pollack *et al.,* where the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5 fold change in mRNA levels. Pollack *et al.,* "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS,* 99(20):12963-12968 (submitted with the Request for Continued Examination mailed 12/21/04).

Orntoft *et al.*, also previously cited by Applicants, report similar findings. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers and found that in

general (18 of 23) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Orntoft *et al.,* in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45 (submitted with the Request for Continued Examination mailed 12/21/04).

Similarly, Hyman *et al.,* previously cited, compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. *See* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research*, 62:62-40-6245 (submitted with the Request for Continued Examination mailed 12/21/04).

Thus, at least these references demonstrate the art recognition of a correlation between an increase in DNA copy number and an increase in mRNA. The majority of the remaining evidence and arguments presented during prosecution, for example those submitted with the Request for Reconsideration filed 12/11/06, have been aimed at demonstrating the art recognition that mRNA levels correlate with protein overexpression levels. The '308 patent discussed herein is direct evidence that the PTO accepts such a correlation for utility. Indeed, claim 1 of the '308 patent makes it clear that the claimed polypeptide is encoded by a nucleic acid that is "amplified in lung or colon tumors."

The Office action attempts to distinguish the references submitted by Applicants along with the Request for Reconsideration filed 12/11/06 on the basis that those references "are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general." Page 6 of the Office action mailed 3/7/07. Applicants respectfully submit that when the evidence of the references is taken as a whole, as it must be, that evidence demonstrates that in general it is more likely than not that there is a correlation between gene amplification and protein overexpression. For example, the Office action distinguishes the teachings

of Alberts and Lewin by acknowledging that although these references disclose that "initiation of transcription is the most common point for a cell to regulate the gene expression" these references also acknowledge such is "not the only means of regulating gene expression." Page 5 of the Office action mailed May 7, 2007 (emphasis added). Applicants do not mean to argue that the central dogma of biology, that DNA is transcribed to mRNA and then translated to protein, is the only means of regulating gene expression. Applicants have admitted there are some instances where gene amplification does not correlate with overexpression. Rather, Applicants only mean to argue that according to PTO standards of demonstrating utility, which the Office action does not dispute requires Applicants only to show the asserted utility is more likely than not true, not necessarily true, Applicants have demonstrated an adequate utility.

In addition, according to the Office action, one reference cited by Applicants, Godbout *et al.* is relevant to establishing the asserted correlation. According to the Office action, Godbout *et al.* teaches that "[t]he DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumours and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." Page 8 of the Office action mailed 3/7/07. Based on this statement in Godbout, the Office action argues that Applicants' assertion of utility is not sufficient because the specification does not teach that the protein encoded by the PRO347 gene would confer any selective advantage on a cell expressing it.

Applicants respectfully disagree that Godbout teaches that amplified genes are *only* overexpressed if they provide a selective advantage. Rather, Godbout, which focuses on *co-amplified* genes, states that "it is unlikely that a gene located ~ 400 kb from the *MYCN* gene will be consistently amplified as an intact unit unless its product provides a growth advantage to the cell." Page 21162 of Godbout. Thus, rather than conclude that an amplified gene must encode a polypeptide that provides a selective advantage, Godbout suggests that the selective advantage plays a role in why a particular gene

may be co-amplified with another gene. Applicants further respectfully submit that this aspect of the Godbout teachings is not relevant to Applicants' assertion of utility, which is not based on any gene that is alleged to be co-amplified. Further, Applicants note that regardless of the co-amplification aspect of the Godbout reference, this reference teaches that a DEAD box gene, DDX1, shows good correlation between gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cancer cell lines studied. *See* pages 21164, 21167, and 21168. Thus, Godbout does not teach that Applicants assertion of utility is wholly inconsistent with or violates any scientific principles nor does Godbout make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility.

The reference and article evidence submitted and relied on by Applicants is further bolstered by the declarations submitted by Applicants, including the two Polakis Declarations and the Scott Declaration. The Office action alleges that the Polakis Declarations are not persuasive because those declarations are directed at establishing the correlation between PRO347 mRNA and protein levels but the specification does not provide any information about the level of PRO347 mRNA. Yet, as noted by the Office action, the specification does disclose that PRO347 DNA is significantly amplified in lung or colon tumors. Specifically, approximately 87% of lung tumor tissues and approximately 53% of colon tumor tissues listed in Table 9 and tested showed greater than 2-fold DNA amplification for PRO347. Applicants have submitted substantial evidence, including the Pollack, Orntoft, and Hyman references discussed above, demonstrating that in general it is more likely than not that DNA amplification levels correlate with mRNA levels. Thus, one of ordinary skill in the art would reasonably conclude that PRO347 mRNA is increased relative to the amplification of PRO347 DNA disclosed in the specification. With that understanding, the Polakis Declarations provide significant, persuasive evidence.

The Office action further attempts to rebut the evidence of the Polakis Declarations by alleging that it cannot be determined whether the declarations refer to the same data, nor why one discusses tumor cells while the other discusses tumor tissue. Applicants

respectfully submit these are not sufficient bases for rebutting the Polakis Declarations. Both declarations state that the basis for the opinion presented therein is Dr. Polakis' experience with the Tumor Antigen Project, which involves analysis of differential gene expression in tumor cells and tissue versus normal cells and tissue. Further, the Polakis Declarations are based on Dr. Polakis' analysis of at least 31 differentially expressed gene transcripts. Applicants respectfully submit this is the correct reading of the Polakis Declarations. Yet, even if one of ordinary skill in the art were to read Dr. Polakis' declarations as referring to different data sets, as the Office action alleges is possible, then Dr. Polakis' declarations are even more persuasive evidence demonstrating that for 62 differentially expressed gene transcripts a correlation was observed between gene amplification and protein overexpression. In addition, Applicants note that the Polakis Declarations were submitted and considered by the PTO in allowing the '308 patent.

The Office action alleges that the Scott Declaration is not persuasive because it sets forth conclusions, not facts, and because it is outweighed by the totality of the evidence. Applicants respectfully disagree. Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue. This conclusion, which states a general rule observed over time is based on the stated facts that Dr. Scott has more than 15 years experience with microarray technologies, and in his experience, Dr. Scott has noticed a good correlation. Applicants respectfully submit that when the Scott Declaration is considered with the other evidence cited by Applicants supporting the asserted utility, as it must be, it is clear that Applicants have met the burden of establishing a utility for the claimed polypeptide. Indeed, Applicants note that the Scott Declaration was submitted along with the response that led to issuance of the '308 patent.

Thus, as recognized by the PTO in issuing U.S. Patent No. 7,208,308, gene amplification is an essential mechanism for oncogene activation and in general gene amplification correlates with protein overexpression. Applicants respectfully submit that consideration of the totality of the evidence clearly demonstrates that Applicants'

asserted utility is specific, substantial, and credible. Applicants have overcome this ground of rejection and respectfully request it be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 27-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a substantial utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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